Exhibit N
Pt. 1

Cover pages for Comments of Ad Hoc Committee on the Safety of Ma Huang (Oct. 10, 1995), 95N-0304, Rep. 1, Vol. 36-38 (listing as attachment F.6: "Dr. Dennis Jones, 'Ephedra Herb in Nutrition', January 26, 1994").

Ad Hoc Committee on the Safety of Ma Huang's Comments (Oct. 10, 1995), 95N-0304, Rep. 1, Vol. 36-38 at Vol. 36, (providing pages 2-30 of "Dr. Dennis Jones, 'Ephedra Herb in Nutrition', January 26, 1994")(original comments attachment does not provide a "page 1").

Ad Hoc Committee on the Safety of Ma Huang
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October 10, 1995

By Hand Delivery

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, Maryland 20857

'95 OCT 11 A9:29

Re: Ephedrine Alkaloids: Reports of Adverse Events; Availability
Docket No. 95N-0304

Dear Sir/Madam:

The Ad Hoc Committee on the Safety of Ma Huang submits the enclosed three-volume report for inclusion in the record of the above-referenced proceeding. A copy of this report was provided to the Center for Food Safety and Nutrition, Division of Special Nutritionals, on July 3, 1995, by hand delivery to Ms. Connie Hardy (HFS-456).

Please contact the undersigned if you have any questions.

Sincerely,

William D. Appler

WDA:lj

Enclosure

95N-0304

RPT1

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D. C.V. of Dr. Wayne Snodgrass.

Sec. 3: Analyses of Complaints Concerning Ephedra Products:

A. Dr. Joseph Borzelleca and Dr. Graham Patrick, Safety of Ephedra/Caffeine Dietary Supplements When Ingested at Labeled Doses by Persons Not Excluded by Label Warnings, February 21, 1995.

B. Drs. Borzelleca and Patrick, A Critical Analysis of Reported Side Effects and Injuries Attributed To Consumption of Formula One, June 29, 1995.

C. Drs. Borzelleca and Patrick, Review of One Death Attributed by TDH to Consumption of Formula One, May 10, 1995.

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F. Excerpt from Letter, James R. Prochnow, Esq., to Ms. Shelly Maifarth, FDA Denver, January 20, 1995, re TDH Alleged Ma huang Side Effects.

G. Expert Witness Statement of Dr. John Todd Bagwell, with Dr. Bagwell's C.V., November 22, 1994.

H. Expert Witness Statement of Dr. Kenneth Blum, with Dr. Blum's C.V., November 23, 1994.

I. Revised Expert Witness Statement of Dr. Marvin J. Rudolph, with Dr. Rudolph's C.V., November 28, 1994.

J. Dr. Dennis Jones, "Market surveillance of effects reported in 230,000 users from ingestion of products containing Ma huang levels giving an intake of 60-120 mg. ephedrine alkaloids per day", June 25, 1995.

Sec. 4: Analysis of FDA's Health Hazard Evaluation.

A. Dr. Dennis Jones, "Analysis on FDA's Health Hazard Analysis of Ephedra/Caffeine Products", June 28, 1995.

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B. FDA Health Hazard Analysis, November 15, 1994.

Sec. 5: FDA-Related Materials, and Documents from the TDH Proceedings and Proposal:

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D. Listings of Products Sold in Texas Containing Ephedra or Ephedra/Caffeine.

E. Excerpt from Deposition of Cynthia Culmo, November 22, 1994.

F. TDH Proposal, 20 Tex. Reg. 2379 (March 31, 1995).

Sec. 6: Miscellaneous Materials:

A. Dr. Dennis Jones, "Ephedra Herb in Nutrition", January 26, 1994.

B. Dr. Dennis Jones, "Ma Huang: The Facts", in Bariatrix, January-February, 1995.

C. Dr. Dennis Jones, "Ma Huang (Herba Ephedra)", March 7, 1995.

D. Dr. Dennis Jones, "Facts About Ma Huang (Ephedra Herb)", March 22, 1995.

E. American Herbal Products Association, Recommended Labeling for Ma Huang Products, March 9, 1994, and Labeling for Formula One, January 1, 1995.

F. Dr. Brian Lebovitz, "Why the FDA Wants to Ban Ephedrine", May, 1995.

G. Declaration of David Litell, Lack of Abuse Potential for Ephedra and Safety Data, June 28, 1995.

H. Kira Hutchinson, "The Use and Availability of Ephedra Products in the United States", February 23, 1995.

I. Robert S. McCaleb, "Perspective on Ephedra Ephedrine and Caffeine Products", Testimony in Texas Hearing, April 28, 1995.

J. Caffeine, "Diagnostic criteria for 305.90 Caffeine Intoxication", Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, of the American Psychiatric Association, Pp. 212-213.

EPHEDRA HERB IN NUTRITION AND HEALTH

Executive summary and conclusions:

Ephedra, also known as Herba Ephedrae and *Ma huang*, has been known to mankind for at least 20,000 years, and it has at various times been used as food, in beverages and for healing purposes. The benefits attributed to this herb have been many, but they all relate to health and wellbeing in a positive sense.

Ephedras are among the oldest and most primitive of plants, scientifically described as gymnosperms, and are leafless except for tiny scales at the joints. The genus includes more than 40 species world-wide. They grow by preference in arid regions, and possibly by virtue of their widespread distribution, almost every culture has a history of their use which persists to the present day. They are also important in animal nutrition in several areas of the world, both for livestock and for wild animals, and thus may occupy an important position in the food chain in areas where they are indigenous.

Their use in traditional medicine goes back at least 5000 years, the main geographical area for these uses being the Far East, particularly China and India, but even in North America there are several hundred years of tradition underlying the use of Ephedra as healing herbs or in refreshing drinks. Though their main historical healing virtues have been associated with respiratory disorders (they were specifically used as decongestants and mucolytic agents), they have recently been found to possess considerable value as adjuncts to *healthy eating* and aids to weight loss. In this respect, medical research into the properties of ephedrine, the main alkaloid present in the Ephedras, has revealed the scientific basis for their use and has done much to explain the quite startling efficacy of herbal remedies based on Ephedra in induction of weight loss.

In particular, recent research has substantiated the view that ephedrine, whether in pharmaceutical form or in the natural form as a herbal remedy, is quite possibly the most appropriate, most effective and safest aid to weight loss. In fact, in the form of the natural herb, ephedrine appears to possess the intrinsic pharmacokinetic properties of slow and smooth absorption which go even further to enhance efficacy and safety.

As noted, ephedrine, and by both extension and directly herbs containing this substance (the Ephedras), has been shown to possess considerable merit as a treatment which facilitates weight loss. The efficacy is increased by combination with other natural substances termed methylxanthines, particularly caffeine, without concomitant increase in the risk of side effects.

Though the best results have been reported when this treatment is administered together with a low calorie diet, use of ephedrine in patients who are free to select their own food (the unrestricted diet) also results in weight loss at a moderate rate.

The action of ephedrine and herbs which contain this substance is shown to be an increase in thermogenesis with increases in Resting Metabolic Rate, increased lipolysis, and in some cases, particularly at higher doses, suppression of hunger and sensations of increased wellbeing. In practical terms, patients losing weight who use ephedrine show significantly increased rates of weight loss, and a greater proportion of the weight lost is from stored fat. The corollary to this, which has also been shown clinically, is that such patients retain lean body mass, and the administration of ephedrine thus has a protein sparing effect. Though it has not been specifically investigated, it also appears that patients on low calorie diets who use ephedrine or herbs containing ephedrine exhibit better compliance, in that there are fewer drop-outs, and are also more likely to reach their target weight.

The dosage levels at which effects are obtained is low, and doses high enough to result in central stimulation do not appear to improve the rate of weight loss, though they may improve the subjective sense of wellbeing of the patients. Since the effects are obtained through modulation, or normalization, of existing mechanisms in the human body, and at dosage levels at which ephedrine itself has no direct actions, the use of ephedrine for this purpose may be considered physiological and not pharmacological, and can be compared to the modulating and normalizing effects of many micronutrients. In fact, the effects of ephedrine at the levels used compare with the effects of high protein diets, and if herbs containing ephedrine were more widely distributed in nature, arguments could be mounted for classification of ephedrine as a beneficial, if not essential, nutrient. The widespread consumption of Ephedra herbs by wild animals and the postulated beneficial effects of these herbs when used as fodder by farm livestock could also indicate an important role of the Ephedraceae in various ecosystems.

No concerns have been expressed about the safety of ephedrine under normal conditions of use; the only reports in the literature of unusual effects relate to the development of psychoses in patients who abused ephedrine-containing products by taking massive doses over long periods of time. Such occurrences cannot be considered as true adverse effects, and it is noteworthy that all symptoms associated with these events rapidly disappeared after the abuse ceased, without any lasting psychological or physical damage. None of the studies reviewed in this document (or those examined but not included) have reported any undue hazard associated with use of ephedrine in reasonable dosages. Concerns of theoretical nature have been discussed and eliminated as of no practical significance, and a number of scientists quoted have stated that though ephedrine is safe, even the theoretical concerns about it could not apply to herbs containing this substance naturally. This latter point has been substantiated by a literature review of references to Ephedra herb, which likewise failed to reveal any safety hazards associated with use of this herb in an appropriate fashion.

The beneficial effects seen with ephedrine in the treatment of obesity and weight problems are achieved at low dose levels, and for this reason, use of herbs containing natural source ephedrine is not only a logical alternative to pharmaceutical forms of ephedrine, but may even be more desirable.

The rationale for this statement lies in the need to maintain levels of ephedrine at the active sites (mainly the synaptic gaps) for long periods. Most pharmaceutical forms are designed to rapidly release their active constituents, so that levels at the active sites fluctuate with the periodicity of the administration. However, active components of herbs are generally released only slowly, and over long periods of time. While a rapid release of ephedrine is undoubtedly desirable for the relief of congestion of the upper respiratory tract, which is the indication for which OTC ephedrine tablets are marketed, it is not desirable for the stimulation of thermogenesis and lipolysis in patients who wish to lose weight. Thus in the latter case, a genuine herbal product which smooths the absorption over a longer period is preferable and could be much more effective.

That this is not only theoretical may be adduced from studies of fake and genuine herbal products, where the onset of action with a fake product (that is, a product which was claimed to contain Ma huang, but actually contained pharmaceutical grade ephedrine, caffeine and phenylpropanolamine) was rapid and dramatic, but short-lived, in comparison with a genuine product.

Historical perspectives:

Ephedra . . . . . has been used for thousands of years in the East (Stuart, 1979).

The oldest current record of man's interest in Ephedra dates back approximately 20,000 years, to the burial of a Neanderthal individual in what is now Iraq (Lietava, 1992). This early ancestor of ours was buried with a number of plants, including Ephedra altissima, and knowledge of the customs of the Middle Paleolithic period, sparse though it is, indicates that this Ephedra must have had considerable significance during life to have merited being interred with the deceased.

Under the name Ma huang, Ephedra has traditionally been used as an invigorating tea or infusion with beneficial effects on respiration in China for more than 5000 years (Stuart, 1979), and the earliest written reference to its use and properties is attributed by some experts to the Emperor, Shen Nung (circa 3100 B.C.) in what may have been the first ever Pharmacopoeia, the *Ben Cao Chien* (others claim that the Shen Nung Ben Cao Chien did not appear until about 100 B.C.). This work was substantially revised and enlarged by Li Shih-Chen (1596). Chinese use of Ma huang (which is correctly the stems of the plant) presently encompasses relief of dyspnoea, the exploitation of the thermogenic properties, the promotion of diuresis and the decongestant properties (Ou Ming, 1989). The roots of the plant also have specific uses, which are distinct from those of stems and leaves.

The Indo-Aryans knew Ephedra as an edible plant that gave strength and happiness, and combated exhaustion (Mahdihassan, 1981). Though Indo-Aryans traditional believed that substances conferring longevity were mainly inorganic, Ephedra was considered as a food with similar beneficial properties (Mahdihassan, 1984), and there is strong evidence that the Rigveda references to *soma* actually describe Ephedra juice (Mahdihassan and Mehdi, 1989). If the Shen Nung Ben Cao Chien was indeed not written until about 100 B.C., then the honour of being the first written reference to the use of Ephedra may fall to the Rigveda (circa 1500 B.C.).

Soma, according to the Rigveda, was the drink of longevity which was even given to newborn infants; this Aryan custom was later to be followed by the Romans, and is still practiced among the Parsee of Bombay and in parts of Iran. Lewis and Elvin-Lewis (1977) also report a long history of use of the dried stems of Ephedra gerardiana in Northern India and Pakistan.

Ephedra was wellknown to the Romans, and was clearly described by Gaius Plinius Secundus in 77 A.D. (see Rackham et al., 1956 - 1966) in his *Natural History*, a work that encompassed 37 volumes, of which 12 dealt solely with the healing properties of plants! It was apparently not widely used in Europe after the times of the Romans (Moritz, 1953), though sporadic references do occur in medieval European literature; Gerard (1597), for example, refers to Herba Ephedrae (presumed to be Ephedra fragilis) as the "Great shrubbie sea Grape".

However, in North America, historical Amerindian use of Ephedra species is well-documented (Moerman, 1986), and includes use of the roots to make bread (Rose, 1972) as well as the stems to make tea (Tyler, 1982). The early settlers may have adopted the latter custom from observation of the Indians, or may have learnt the virtues of such teas from early Chinese immigrants, since during the last 150 years, various Ephedra species have enjoyed use in North America as herbal teas, under names as varied as Mormon Tea, Teamster's Tea, Settler Tea, Squaw Tea, Cowboy Tea, Canutillo, Popotillo, Desert Herb and Ma Huang (Saunders, 1920; Kowalchik and Hylton, 1987). To quote from Saunders (opus cit.):

> *Throughout the arid and semi-desert regions of the Southwest from New Mexico to Southern California, a peculiar plant called* **Ephedra** *by the botanists is abundant. There are several recognized species but all have so strong a family resemblance that in popular parlance they are lumped as one and spoken of as Desert Tea or Teamster's Tea. . . . . Desert Tea was first adopted by the white explorers and frontiersmen as a medicinal drink, supposed to act as a blood purifier and to be especially efficaceous in the first stages of venereal diseases; but its use at meals as an ordinary hot beverage in substitution for tea or coffee is by no means uncommon, and cowboys will sometimes tell you they prefer it to any other.*

Though Ephedra was also used conventionally as a herb or dietary supplement, or even as food, the pleasant, piney tea, frequently prepared from Ephedra trifurca (Lewis and Elvin-Lewis, 1977) was widely used by Mexicans, Indians and settlers alike, even to the extent of regularly being served in brothels ("Whorehouse Tea")!

In conclusion, therefore, one may safely say that the Ephedra herb has a long and well documented history of use, both in food applications and for its healing properties. These uses have not given rise to any cautionary notes on adverse effects, and none of the historical documents that are still available make any reference to negative aspects related to ingestion of Ephedra in either native state or processed form.

Comparative nutrition:

Ephedra not only has a long history of use as a food and a traditional healing plant, but it has also played important roles in animal nutrition. According to the USDA, in the 1930's (USDA, 1937), Ephedra nevadensis and Ephedra viridis were the most important forage ephedras in the United States, and they were described as palatable to all classes of livestock. There are no reports that consumption of Ephedra has adverse consequences for livestock, even at high levels, and in Yugoslavia consumption of Ephedra campylopoda by sheep is considered to increase yields of milk (Kovacevic et al., 1974). Investigation of this particular plant revealed only 6% crude protein but high digestible energy (opus cit.), and with our current understanding of the mode of action of the ephedrine-group alkaloids found in the Ephedraceae, there is little doubt that use as animal fodder would increase the Food Conversion Efficiency of domestic livestock. This would improve milk yields, and also give better rates of weight gain, with leaner carcasses, in meat animals.

Wild animals also consume various species of Ephedra freely. For example, Neotoma devia, a species of woodrat indigenous to Northern Arizona, eats predominantly Ephedra epidermis (Dial, 1988), while paleozoological studies have shown that the diet of the Shasta ground sloth, Nothrotheriops shastense, an extinct species from Arizona, contained large amounts of Ephedra nevadensis (Mormon Tea) and was thus not vastly different from the diets of extant desert herbivores (Hansen, 1978). Other studies have shown that the population dynamics of certain rodents in Mongolia correlate directly with changes in growth patterns of indigenous Ephedra species, denoting the importance of these plants as a food source (Knyazev et al., 1991).

An interesting curiosity is that when given free choice, the honey-bee (Apis mellifera) prefers pollen from Ephedra mellifera (Schmidt and Johnson, 1984). Pollen analysis has also shown reliance of bees on Ephedra species in other arid parts of the world (Riciardelli d'Albore, 1980).

Ephedra in modern times:

Though we know nothing of the uses to which Stone Age man put Ephedra, we may assume that he used it for some healing or nutritional virtue, since these two facets of its use are reflected in the Chinese and Indo-Aryan traditions respectively.

The Indo-Aryans viewed Ephedra as a food that vitalized, and this attribute of the herb was also the main reason why the value of Ephedra as an enervating tea-like drink was recognized in 19th Century North America. Amerindians, though they also recognized, and utilized, this aspect of the herb, pragmatically used the roots as a staple food with no particular virtues implied. Both these nutrition-related aspects are seen in current food uses of the herb. For example, Tanaka (1976), who classifies the Ephedras as edible (food) plants, summarizes the various ways in which they are used as preparation of drinks from the stems, use of seeds to make flour and use of the fruits as such. More recently, Ephedra (as Ma huang) became popular as a non-toxic and non-addictive substitute for caffeine in energizing drinks and products (Dharmandra, 1984), and over the last 15 years hundreds of Ephedra-based products have entered the marketplace for use as such products.

Despite the fact that most users of Ephedra-based products consume them for the energy and vitality boosting effects, as an alternative to tea or coffee, other nutritive uses have not been neglected, and Ephedra continues to be regarded as a conventional food in various parts of the world. For example, the CSIR (1952) identified Ephedra gerardiana as one of the resource plants of India, and noted the food uses of the fruit, while Katiyar et al. (1990) also report that the berries from Ephedra gerardiana are normal dietary constituents for tribes in the North-Western range of the Himalayas. Certain types of regional foods rely on Ephedra (Beketaeva et al., 1979), and the herb has also been characterized as possessing a harmonious combination of trace elements, vitamins and other biologically active substances in ratios optimal for a human organism (Gerasimova and Barelko; 1980). Interestingly, among desert plants, Ephedra species have extremely high Vitamin C levels (150 mg/100 grams), which make them a major contributor to vitamin requirements of humans subsisting on the local food flora (Grebinskiĭ and Yaroshkin, 1953).

Thus the Indo-Aryan attitude to Ephedra has persisted through to modern times, and this herb continues to be widely used for its food aspects alone. In fact, it could be postulated that use of Ephedraceae as food may favour survival in harsh climates (Vallerand, 1993), firstly because of the thermogenic effects (protection against cold) and secondly because of protein-sparing effects (improved utilization of available food).

The Chinese viewed Ephedra solely as a healing herb with merit in the treatment of respiratory conditions (though they also used the roots, which contain anti-hypertensive substances, for other purposes), and this aspect of the Ephedra herb finally drew the attention of scientists in the late 19th Century. By the mid 20th Century, Ephedra, mainly of Chinese and Indian (now Pakistan) origin, had become an important source of the alkaloids ephedrine and pseudoephedrine, much used in cough and cold remedies.

The medical uses of these alkaloids can thus trace their development back to the original isolation of ephedrine itself from Ma huang towards the end of the 19th Century, and the subsequent thorough investigation of its properties in the early 20th Century (Chen, 1925; Gaignault et al., 1982).

Ephedrine and pseudoephedrine are now mainly manufactured synthetically, since their use in a variety of over-the-counter remedies requires amounts of raw materials that could never be produced from natural sources; in fact, pseudoephedrine and ephedrine together rank close to the top of pharmaceutical raw material manufacture in terms of tonnage, which may serve to illustrate the extent of their use. However, much is known about the compositions of the various members of the genus from research performed at about the time of the Second World War (see for example, Alberti, 1939), and from more recent studies in a large number of countries (see for example Abdel-Wahab et al., 1961) where extraction of natural products remained a viable alternative to chemical synthesis.

The exigencies of the early half of the 20th Century also stimulated attempts to cultivate Ephedra species in North America, and the acquisition of considerable amounts of agronomic and compositional data (Christensen and Hinde, 1936, 1939). These attempts were successful, but also revealed that Ephedras growing in the wild generally give higher yields of alkaloids. Another result of the studies was the naturalization of foreign Ephedras in North America, so that in addition to the indigenous American Ephedras, Ephedra sinica and other exotic Ephedras may also now be found in the wild in North America.

The situation changed significantly in the early 1980's. Up to that time, Ephedra was viewed in two distinct ways; the protagonists of the Indo-Aryan tradition, knowingly or unknowingly, merely used Ephedra as an invigorating food, without really being aware of the properties of the ephedrine-group alkaloids, while the supporters of the Chinese tradition either viewed Ephedra as a potential phytopharmaceutical plant to be processed into sources of raw material for the pharmaceutical industry or as a gentle, natural and non-toxic alternative to ephedrine and pseudoephedrine when a decongestant was required..

In fact, though Ephedra as a herb is practically devoid of toxicity (Dharmandra, 1984; Minamatsu et al., 1991) and can only be abused under the most bizarre circumstances, both ephedrine and pseudoephedrine are themselves of low toxicity, and when presented in pharmaceutical dosage forms they act much more rapidly. Since self-medication sufferers from respiratory disorders generally require rapid relief for acute episodes, the pharmaceutical products have gradually overwhelmed the natural alternative in this particular marketplace.

However, a new use for Ephedra herb was perceived at this time, and far from being a disadvantage, the slower absorption but longer lasting duration of effect from the natural product proved to be a major advantage for this particular use, namely the use as a natural aid to promote weight loss, either alone or as and adjunct to diet programmes. The extremely low incidence of unwanted reactions (estimated in retrospect at less than 20 per 100,000 patients), which were furthermore never of serious nature, also favoured the use of the natural herb for this indication.

Ephedrine in pharmaceutical presentations had been used as an anorexic agent in the 1970's (Sapeika, 1974; Stauffacher, 1975), and though it proved safer than phenylpropanolamine and the amphetamines (Glick et al., 1987; Forman et al., 1989), it was not superior in terms of appetite (hunger) suppression, which was the only mechanism that was thought, at that time, to be of importance. It was therefore little used, until a major research group showed that it possessed pronounced thermogenic properties and became particularly effective when combined with caffeine (Malchow-Moller et al., 1980, 1981; Roed et al., 1980; Stockholm and Hansen, 1983). It was later shown that the thermogenic effect, far from fading away with time (tachyphylaxis), actually became more pronounced (Astrup et al., 1985, 1986).

Though it took some time for these findings to cross over from the strict world of pharmacology to the distinct world of the herbalist, their significance was eventually realized, and a new use for Ephedra herb developed (Bergner, 1993; Jones and Egger, 1993).

Currently, much of the literature and research findings supporting the use of Ephedra herb as an adjunct to weight loss programmes is based on studies with the active principle, ephedrine itself, and these studies also provide the explanation for the synergistic effects seen when Ephedra is taken together with one or more herbs containing caffeine and/or salicylates. Thus, though explanations of mechanisms and actions are derived from studies of the pure constituents, they can logically be extrapolated to the use of the constituents in the form of the natural herbs. This also applies to evaluation of safety, and the only rider to be applied is that absorption of active constituents from the natural herbs is generally slower and shows a smoother pattern.

Ephedra and ephedrine in weight loss:

Malchow-Moller et al. (1980, 1981) published reports of the first study in which a product containing ephedrine was shown to significantly increase weight loss in patients on a diet, in comparison to patients who received only a placebo product. Their double-blind study encompassed 132 patients who were 20% - 80% over their ideal weight, randomized to 3 groups receiving either ephedrine with caffeine, diethylpropion, or placebo. All patients were also given a 1200 kilocalorie diet. A total of 108 patients completed the study, which lasted 12 weeks, and median weight loss in the two treatment groups was significantly better ($p < 0.01$) than in the placebo group:

Placebo - - - - - - - - - - - -	4.1 kg in 12 weeks (n = 31)
Ephedrine plus caffeine - - -	8.1 kg in 12 weeks (n = 38)
Diethylpropion - - - - - - - -	8.4 kg in 12 weeks (n = 39)

Interestingly, there were more drop-outs in the placebo group, and no serious adverse effects were seen in the treatment groups.

The clinical applications of ephedrine were followed, *inter alia*, by Pasquali and his team. An initial study in unselected patients (Pasquali et al., 1985), failed to show significant differences in weight loss between patients receiving placebo and those receiving ephedrine (75 or 150 mg per day), but indicated that ephedrine could be of value under certain conditions. The investigators therefore performed a double-blind cross-over randomized study (Pasquali et al., 1987) in 10 selected adult overweight and obese (body mass index greater than 27) women who had been adapted to low-energy intake for a long period of time and who had plateaued (shown difficulty in losing weight with conventional hypocaloric treatment). Combined with diet therapy (1000-1400 kcal/day), L-(-)-ephedrine hydrochloride (50 mg three times a day per os) or placebo were administered daily before each meal, after a period of stabilization with diet only for 1 month. Each pharmacological treatment lasted for 2 months. Weight loss was significantly greater during the ephedrine treatment period than during the placebo period (2.41 ± 0.61 kg vs. 0.64 ± 0.50 kg, $p < 0.05$). None of the patients presented clinically important side-effects.

In a further study (Pasquali et al., 1992), performed in 10 obese subjects on a 6-week very low calorie diet programme (1965 kJ, 60 g of protein, 45 g of carbohydrates), L-(-)-Ephedrine hydrochloride (50 mg three times a day by mouth) or placebo were administered during 2-week periods (weeks 2 - 5 of the VLCD programme) in a randomized, double-blind, cross-over design.